with the patient by the prescribing physician. Cyclosporine is effective in the treatment of psoriasis, but hypertension and decreased renal function are common sequelae; thus, only patients with severe disease warrant its administration. As with methotrexate, a prompt and often severe rebound can occur after treatment is discontinued. Systemic administration of corticosteroids should never be used in treatment, except in the rare patient with severe, life-threatening psoriasis.

Combination Therapies

Combination therapy permits the use of lower doses of the individual components, thus decreasing their individual toxicities. Combination therapy may include the concurrent use of a topical preparation, such as calcipotriene ointment, with either a phototherapy or systemic therapy, or the use of a systemic agent, such as acetretin, with a phototherapy. For most patients with moderate to severe psoriasis, combination therapy is more effective and less hazardous than monotherapy.

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The Pathogenesis of Kaposi's Sarcoma

KAPOSI'S SARCOMA (KS) HAS received immense attention since 1981 when it was first recognized as a major manifestation of the Acquired Immune Deficiency Syndrome (AIDS). Four forms have been described: an indolent, endemic form seen most commonly in older Mediterranean men; a second form seen in tropical Africa commonly affecting children; an "iatrogenic" form that occurs in individuals receiving immunosuppressive therapy such as organ transplant recipients; and the form associated with HIV infection. Skin lesions are similar in all groups and all appear similar histologically. Vascular endothelial cells are thought to be the cell of origin of KS on the basis of morphology, presence of vascular spaces, ultrastructural appearance, and the expression of various endothelial markers.

The true nature of KS is a subject of intense study. Whether KS is a clonally derived malignancy or a proliferation of spindle cells in response to local cytokines has been a subject of controversy. High local levels of cytokines including interleukin 6 (IL-6), basic fibroblast growth factor (bFGF), tumor necrosis factor α (TNF-α), interferon γ and vascular endothelial growth factor (vEGF) have been shown to be present in KS lesions. Interleukin-6 is produced by KS spindle cells themselves and exogenous IL-6 has been shown to enhance the proliferation of KS cells in culture. Other features that favor a proliferative rather than truly neoplastic process include the fact that there are often many lesions that develop simultaneously without a characteristic primary lesion and the absence of a tendency to spread regionally to local lymph nodes. Furthermore, lesions often resolve when the patient's immunocompetence is reconstituted. On the other hand, a recent article demonstrated clonality of KS lesions with identical genetic sequences in different KS lesions in the same patient. This does not necessarily prove that KS develops from a primary lesion and spreads throughout the body, however.

An infectious etiology for KS has been sought for over 3 decades. In 1994 Chang and Moore discovered herpes-like DNA sequences in KS tissues from patients with AIDS. These sequences were not identified in tissues from normal hosts, lymph nodes, peripheral lymphocytes infected with Epstein Barr virus (EBV), DNA extracted from other vascular tumors, or other tissues involved with AIDS opportunistic infections. These DNA sequences are partially homologous to gene segments of γ-herpesvirinae such as *Herpesvirus saimiri* and EBV. This novel herpesvirus associated with KS was thus classified as a γ-herpesvirinae and called Kaposi's sarcoma-associated herpesvirus (KSHV) or Human Herpesvirus-8 (HHV-8).

Since HHV-8 was discovered, researchers have sought to prove that the virus is truly the cause of KS and not simply a co-factor. Three bodies of evidence suggest causality. First, HHV-8 is present in all types of KS and is present in virtually all samples tested to date. Second, serologic studies show that the prevalence of HHV-8 infection in various geographic and risk-group populations parallels the incidence of KS in these populations. Third, both polymerase chain reaction (PCR)-based detection of HHV-8 DNA in peripheral blood and antibody seroconversion studies show that HHV-8 infection occurs before the development of KS and is highly predictive of its development.

Current research aims to define the role of HHV-8 in initiating the pathogenesis of KS lesions. Several potential oncogenes have been identified that allow the virus to avoid antiviral responses such as cell-cycle arrest, apoptosis and enhanced cell-mediated immunity, any of which could lead to abnormal cell proliferation.

The current treatment options for all forms of widespread or systemic KS include cytotoxic drugs (bleomycin, vinca-alkaloids, anthracyclines and taxol), systemic interferon and radiotherapy. Overall, conventional chemotherapy and radiation are only partially effective and have significant adverse effects. Novel approaches that take into account the recent discoveries of molecular factors that produce KS lesions are already in development. Drugs that diminish angiogenesis in KS have been shown to be at least partially effective in preliminary studies. For example, thalidomide, a drug that blocks angiogenesis in developing limb buds, has been reported to induce regression of KS lesions in some

patients. Antiviral agents that with activity against HHV-8 such as foscarnet, ganciclovir and acyclovir are also currently being investigated and preliminary results indicate that foscarnet may cause remission of some KS lesions. Furthermore, KS lesions in HIV-positive individuals often resolve after initiation of treatment with Highly Active Antiretroviral Therapy (HAART) that includes 2 nucleoside reverse transcriptase inhibitors and a protease inhibitor. Although HAART may have some antiviral activity against HHV-8, it is likely that the effect is related to improvement in the patient's immunity. This is analogous to the regression seen in KS that develops in transplant patients when immunosuppression is stopped.

Thus, the cause and pathogenesis of KS are becoming clearer. As a consequence, new and more effective treatments are being developed.

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Dermatoses of Pregnancy

MANY CUTANEOUS CHANGES occur during pregnancy, including pigmentary (linea nigra, melasma, darkening of nevi), glandular (increased eccrine and sebaceous gland function, decreased apocrine function), and vascular (spider hemangiomas, palmar erythema, pyogenic granulomas). About 1.6% of women will develop pruritus during pregnancy. Five dermatoses are specific to pregnancy: pruritic urticarial papules and plaques of pregnancy (PUPPP), herpes gestationis (HG), cholestasis of pregnancy (pruritus gravidarum), impetigo herpetiformis and linear IgM dermatosis of pregnancy (LMDP). Some authors prefer the term "polymorphic eruption of pregnancy" (PEP) to encompass PUPPP, prurigo of pregnancy and pruritic folliculitis of pregnancy.

PUPPP occurs in approximately 1/240 pregnancies, mainly in primigravidas in their third trimester, and is characterized by intensely pruritic urticarial papules and plaques. The lesions typically begin in the striae on the lower abdomen, sparing the periumbilical area, and later spread to involve the breasts, back, and extremities. Pinpoint vesicles may be present, but bullae should raise the clinical suspicion for HG. The latter is confirmed by direct immunofluorescence testing (which is negative in PUPPP). There is no associated fetal morbidity or mortality, but the pruritus is often intractable. The eruption resolves spontaneously shortly after delivery. Although the etiology is unknown, it has been postulated to be related to abdominal distention, and cases involving twin and triplet pregnancies are common. Treatment includes topical steroids and oral antihistamines, but oral corticosteroids may be required in severe cases.

Prurigo of pregnancy may be a distinct entity, or it may represent an unusual variant of PUPPP. It occurs in approximately 1/300 women, with an onset in the 25th–30th week of pregnancy. Itchy, grouped, excoriated papules develop primarily on the extensor surfaces of the extremities in patients with an atopic diathesis. Treatment is symptomatic, and there is no associated fetal morbidity or mortality.

Pruritic folliculitis of pregnancy is most likely a form of acne/folliculitis that occurs in pregnancy due to hormonal alterations. Patients in their 4th–9th month of pregnancy develop generalized, excoriated follicular papules and sterile pustules that resolve shortly after delivery. Mid-potency topical corticosteroids and oral antihistamines have been used but without significant benefit in most patients.

HG occurs in 1/7000 pregnancies. Patients develop severely pruritic, urticarial plaques and tense bullae on the trunk and extremities. The umbilicus is commonly involved. The disease usually requires systemic corticosteroids and may persist for months or years after delivery. A postpartum flare occurs in 75% of patients, and approximately 25% flare with oral contraceptives or menses. About 5% of patients' newborns will have transient blisters; there is an increased risk of prematurity and a tendency for small-for-gestational-age babies. The disease commonly recurs in subsequent pregnancies. In contrast to PUPPP, direct immunofluorescence is positive, revealing linear C3 along the basement membrane zone in 100% of patients.

The incidence of cholestasis of pregnancy varies widely in different countries and ethnic groups. The incidence in North America, for example, is approximately 1/1293, while in Chile and Scandanavia it occurs in 3% to 14% of the population. In this disorder, patients develop severe generalized pruritus, in the absence of primary lesions. The degree of pruritus directly correlates with the level of serum bile acids, which is often markedly elevated. Symptoms begin in the late 2nd to early 3rd trimester and usually resolve within 48 hours of delivery. There is often mild elevation of liver function tests, but if the bilirubin is normal, the disease is referred to as "pruritus gravidarum." Treatment has included phenobarbital, cholestyramine, and ion exchange resin, often without significant benefit. The disease may recur in subsequent pregnancies.

Impetigo herpetiformis has been infrequently reported in the literature. Patients in their third trimester develop generalized pustules on a background of erythema and scaling. The eruption may be accompanied by fever, nausea and vomiting, and leukocytosis. If the patient develops hypocalcemia, she may develop tetany, seizures, and delirium. Because of placental insufficiency, there is an increased risk of stillbirth. The disease remits promptly after delivery. Because of its clinical resemblance to pustular psoriasis and the extremely low levels of skin-derived antileucoproteinase found in patients, this disease is felt to represent a variant of pustular psoriasis.

LMDP is also rarely reported. It occurs in the 3rd trimester as pruritic, red, follicular papules on the trunk